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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/675,509	FULTON ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1, 3, 10, 11, 16-31* is/are pending in the application.

4a) Of the above claim(s) *16,17 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10,11,18,19 and 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/20/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/04 has been entered.

Applicants' amendment, filed 4/27/05, has been entered. Claim 25 has been amended. Claims 1, 3, 10, 11, 16-31 are pending. Claims 16, 17, 20-24 are withdrawn. Claims 1, 3, 10, 11, 18, 19, 25-31 are under current examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 10, 11, 25-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim1-7, 15-20 of copending Application No. 10/342,119. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods for inducing apoptosis in a selected group of cells by administration of thiaminase. The instant claims are directed to methods of inducing thiaminase in vertebrate cells *in vivo*, by either administering a thiaminase or derivative thereof, or a non-pathogenic bacterium comprising a recombinant nucleic acid encoding the thiaminase, to reduce levels of thiamin to induce apoptosis. In specific embodiments, the instant claims are directed to expression vectors comprising the recombinant nucleic acid sequence, and bacterium which comprise this recombinant nucleic acid sequence. The '119 claims are directed to methods of inducing apoptosis of a selected group of vertebrate cells by reducing the level of thiamin in the cells; particularly, wherein the thiamin-depleting agent is a thiamin-cleaving compound. The '119 claims are further directed to compositions for the delivery of the nucleic acid sequence, and pharmaceutical compositions comprising the thiamin-depleting agent.

Thus, given that the instant application teaches the same methods of inducing apoptosis, and that a thiaminase is considered a thiamin-cleaving agent, further, that both methods are directed to reducing levels of thiamin to induce apoptosis, the claims are obvious over each other. Finally, the '119 claims, wherein

specific embodiments are directed to compositions for delivery, and pharmaceutical compositions, the instant claims are encompassed by these embodiments, as the bacterium containing the nucleic acid are considered a composition for delivery or pharmaceutical compositions, because delivery of the bacterium is what is instantly claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 25-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record advanced in the prior Office action, mailed 2/4/03. This is a new matter rejection, as set forth in the prior Office action, pages 3-6.

Applicants argue that, in the prior Office action, the Examiner set forth that the claims require non-pathogenic bacterium, which are not described in the instant

disclosure; particularly, that Clostridium and Salmonella are known in the art to be pathogenic. Applicants submit that, as described below, the bacteria in the preferred embodiments are attenuated or genetically modified to be non-pathogenic. Applicants point to the specification to show several non-pathogenic bacteria, and cite reports from the literature in which they are employed in cancer therapy. See p. 6, 1st full ¶ of the Response. Applicants argue that the Examiner concedes that the specification teaches the construction of a vector adapted for expression in prokaryotic cells, and that the specification provides description of non-pathogenic bacteria in cancer therapy. Furthermore, Applicants argue that how to engineer an attenuated Salmonella strain to express thiaminase for an anti-tumor therapy and its delivery is described. Therefore, Applicants argue that the construction of a non-pathogenic bacterium comprising a nucleic acid, encoding a thiaminase, in conjunction with the specific teachings in the specification of how to use the bacteria, are sufficiently described by the specification. See pp. 6-7 of the Response.

Applicants' arguments have been considered, but are not persuasive. Applicants are arguing limitations that are not in the claims. In particular, that the "preferred embodiments" which genetically modify the bacteria to be non-pathogenic are not found to overcome the breadth of the claims, which introduce new matter to the disclosure. The claims require that the bacterium are non-pathogenic; however, there are no steps with regard to the genetic modification or attenuation of the bacteria in the claims, such that it is readily apparent that this

causes the bacteria to be non-pathogenic. Applicants point to the specification, page 35, lines 1-11 for support that the specification describes "non-pathogenic" bacteria. The specification only discuses utilizing Salmonella as a living vector, and the, "extensive knowledge of the pathogencity of this species." See #7, line 11. There is no evidence that the attenuated species that this produces a non-pathogenic bacteria. Applicants point to p. 36, lines 3 to page 37 with regard to Clostridium, and the genetic engineering of these bacteria to express specific enzymes. Although the specification may provide guidance with regard to transfecting specific prokaryotic cells, there is no specific description with regard to the "non-pathogenic bacteria" as encompassed by the claims. The breadth of these claims encompass bacteria that are non-pathogenic prior to transfection and bacteria that (as asserted by Applicants) are made non-pathogenic by genetic modification or attenuation.

Thus, it is maintained that these amendments introduce new matter into the disclosure, and that the claimed invention as a whole is not adequately described if the claims require essential, or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing with sufficient, relevant, identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.,* 48 USPQ2d

1641, 1646 (1998). In the instant case, the claimed embodiments of non-pathogenic bacterium comprising a recombinant nucleic acid sequence encoding a thiaminase, and methods of using such bacterium for inducing apoptosis in vertebrate cells, lacks written description. The specification fails to describe any non-pathogenic bacterium that would fall into this genus and could be constructed and used as claimed, and it was unknown, as of Applicants' filing date, that any of these non-pathogenic bacterium would be able to induce apoptosis.

Applicant is reminded that *Vas-Cath Inc. v.* Mahurkar, 19 USPQ2d 1111 [Fed. Cir., 1991] makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The prior rejection of claims 1, 3, 11, 18, 19, 25-31, is *maintained*, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record advanced in the prior Office action (mailed 2/4/03).

Applicants argue that the specification fulfills the written description requirement with reference to structural properties of thiaminase. Applicants argue that the amino acid sequences from N. gruberi and B. thiaminolyticus are presented in Figures 5 and 8, and that two other structural properties are describes;

namely the active site and the six amino acid sequence (GYSESM) which is part of the pyrimidine coordinate residues. Applicants argue that given the two exemplary thiaminase sequences and structural motifs described above, one of skill could easily find analogous sequences in any public databases using sequence analysis. See p. 8 of the Response.

This is not persuasive. The claims are directed to a thiaminase, undescribed derivatives of a thiaminase, and sequences that are variably identical to a thiaminase (see claims 28-31). Although thiaminase I from *N. gruberi*, as encoded by SEQ ID NO: 3, has been adequately described, as set forth in the prior Office action, there is no specific description provided by the specification for any other derivatives or sequences with specific percentage identity (e.g., 35 or 50%) to SEQ ID NO: 4 (see claims 28), which, when constructed and used as claimed, would be capable of inducing apoptosis in vertebrate cells.

Applicants argue that the specification provides adequate written description of derivatives of thiaminase I from N. gruberi, and that these derivatives are described structurally with respect to their homology and length, relative to N. gruberi thiaminase I, and that given the amino acid sequence of N. gruberi, the homology and length requirements present in the specification, and the routine nature of amino acid or nucleic acid comparison in the art, one would readily recognize a thiaminase derivative as meeting those requirement. See p. 8, 2nd ¶ of the Response.

This is not persuasive. The specification provides general teachings with regard to nucleic acid sequences that have varying percentages of homology or sequence similarity to a thiaminase gene. However, absent factual evidence, a percentage sequence similarity of less than 100% is not deemed to reasonably support one skilled in the art as to whether the biochemical activity of the claimed subject matter would be the same as that of a similar, known biomolecule. It is well-known for nucleic acid, as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an undescribed biomolecule that may or may not correspond to the structure and function of the claimed nucleic acid. For example, there is no description with regard to the "derivative" of a thiaminase, that when constructed and used as instantly claimed, would induce apoptosis. Thus, it is maintained that, other than SEQ ID NO:3, which encodes thiaminase I from *N. gruberi*, the instant specification fails to provide description for any other thiaminases, or any derivatives thereof.

As such, the claimed invention does not meet the written description requirement in that the specification does not provide a description of the claimed invention with all its limitations, as stated in MPEP §2163, for example, figures, diagrams, formulas or structures, etc. Although the specification contemplates that

the thiaminases from other organisms would be "anticipated" to be clear homologues, the specification does not provide sufficient description with particularity to indicate that Applicants had possession of the claimed invention. In particular, the specification fails to meet the written description requirement with regard to the claimed embodiment of nucleic acid sequences encoding thiaminases or derivatives thereof isolated from species other than *N. gruberi*, or nucleic acid sequences encoding derivatives of thiaminase I isolated from from *Naegleria gruberi* lacks written description.

It is reiterated that the specification has only provided adequate written description of a nucleic acid encoding thiaminase I from *N. gruberi*. The specification fails to adequately describe the broad genus encompassed by the term "thiaminase". It is reiterated that the skilled artisan cannot envision all thiaminases genes isolated from species other than *N. gruberi*, or nucleic acid sequences encoding derivatives of thiaminase I isolated from *Naegleria gruberi;* therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. Therefore, as no nucleic acid sequences encoding thiaminases or derivatives thereof isolated from other species, or nucleic acid sequences encoding derivatives of thiaminase I, other than SEQ ID

NO: 3, isolated from *Naegleria gruberi*, they do not meet the written description provision of 35 U.S.C. § 112.

Applicants argue that the specification provides sufficient guidance with regard to how non-pathogenic bacteria which comprise a recombinant nucleic acid for inducing apoptosis because the specification provides guidance with regard to non-pathogenic bacteria which may be used to deliver thiaminase to a tumor. See p. 9, 1st ¶ of the Response, and above.

This is not persuasive. The specification does not provide sufficient description with regard to the embodiment of "non-pathogenic" bacteria, the passages cited by Applicants are to pathogenic bacteria, which are rendered non-pathogenic by virtue of either attenuation or genetically modified bacteria. Thus, there is no written description for any non-pathogenic bacteria which, when used as instantly claimed, would induce apoptosis in vertebrate cells or methods for delivering a thiaminase or derivative thereof to vertebrate cells *in vivo*. Accordingly, as the specification does not disclose such bacterium or uses of said non-pathogenic bacterium, they do not meet the written description provision of 35 U.S.C. §112.

The prior rejection of claims 1, 3, 11, 26-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 3, which encodes thiaminase I from *Naegleria gruberi*, vectors containing a nucleic

acid sequence encoding thiaminase I from *Naegleria gruberi* operatively linked to a promoter, and cells transformed *in vitro* by said vector, and bacterium comprising a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi,* the specification does not reasonably provide enablement for methods of inducing apoptosis in a selected group of vertebrate cells *in vivo,* comprising administering to a vertebrate a thiaminase or derivative thereof or a non-pathogenic bacterium comprising a nucleic acid molecule encoding said thiaminase or derivative targeted to said selected group of vertebrate cells, thereby reducing the level of thiamin in said cells sufficiently to induce apoptosis of said cells, methods for delivering a nucleic acid sequence encoding a thiaminase or derivative to vertebrate cells *in vivo,* eukaryotic cells that have been transformed with a eukaryotic expression vector comprising a nucleic acid sequence encoding a thiaminase derivative *in vivo,* or non-pathogenic bacterium encoding a recombinant nucleic acid sequence encoding a thiaminase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that, with regard to the enablement rejection, gene therapy is known to those of skill in the art, wherein a defective gene is replaced by a functioning copy of that gene. Applicants provide Encyclopaedia Britannica which defines gene therapy as, "introduction of a normal gene into an individual in whom the gene is not function, either into those tissue cells that normally express the

gene, or into an early embryonic cell." Applicants argue that the pending claims neither recite the replacement of a defective gene into cells, nor the transfection of cells with a gene in order to achieve the desired result of inducing apoptosis in those cells. See p. 9 of the Response.

This is not persuasive. The claims broadly encompass gene therapy, because they are directed to the introducing a bacterium transfected with a gene in order to express that gene of interest, to an individual. Thus, the prior art of record (cited in the Office action mailed 5/28/02) are germane to the instant invention. The invention requires the delivery of thiaminase to appropriate cells in order to induce apoptosis. The specification fails to provide guidance or working examples with regard to the unpredictabilities associated with gene therapy, which, as outlined in prior Office actions, include utilizing a particular vector, introduction of particular cells, the regulation of the transgene expression, any unpredictable side effects due to ectopic expression of the transgene in normal tissues, the amount and stability of the protein produced. These unpredictabilities are art-recognized in gene therapy, both *in vivo* and *ex vivo*. Furthermore, it is reiterated that the specification fails to teach with particularity, which cells would be target cells for targeted thiaminase expression, how those target cells would be specifically contacted (*i.e.*, is a particular promoter or route of administration critical), and further, how to control apoptosis *in vivo* such that only targeted cells (and not other cells) would be destroyed.

Furthermore, with regard to the recitation of "non-pathogenic bacterium", it is noted that the specification provides no teachings or guidance as to what non-pathogenic bacterium could be constructed and used as required by the claims. It is maintained that the specification is not enabling for teachings with regard to non-pathogenic bacterium, as instantly claimed.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving thiaminase gene therapy, the lack of guidance or direction provided by the specification to carry out thiaminase gene therapy as broadly claimed, the lack of working examples provided by the specification for the demonstration or correlation to inducing apoptosis or achieving therapeutic thiaminase gene expression *in vivo*, the unpredictable and undeveloped state of the art with respect to the gene therapy art, it would have required undue experimentation for one of skill in the art to make and/or use the claimed vectors, bacterium, and methods of using the same.

Claim Rejections - 35 USC § 112

The prior rejections under 112, 2nd ¶ are withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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